NMCP COVID-19 Literature Report #73: Friday, 30 July 2021

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Purpose: These reports, published every other week on Fridays, are curated collections of current research, evidence reviews, special reports, grey literature, and news regarding the COVID-19 pandemic that may be of interest to medical providers, leadership, and decision makers.

All reports are available online at https://nmcp.libguides.com/covidreport. Access is private; you will need to use the direct link or bookmark the URL.

Disclaimer: I am not a medical professional. This document is current as of the date noted above. While I make every effort to find and summarize available data, I cannot cover everything in the literature on COVID-19. Please feel free to reach out with questions, suggestions for future topics, or any other feedback.

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In Memoriam

Dr. Paul Auerbach, an emergency care physician who pioneered the field of wilderness medicine and literally wrote the book on the subject, has died of brain cancer at 70 (NYT).

> "I kept going back to literature to read, but there was no literature," he said. "If I wanted to read about snake bites, I was all over the place. If I wanted to read about heat illness, I was all over the place. So I thought, 'Huh, maybe I'll do a book on wilderness medicine.'"

The Big Picture

News in Brief

"97% of people entering hospitals for COVID-19 are unvaccinated" (NPR).

"Southeast Asian countries struggle to contain a devastating third wave of COVID-19" (NPR).

"A new way to visualize the surge in Covid-19 cases in the U.S." (STAT).

Mortality

"The US life expectancy dropped by 18 months due to COVID-19, according to the Centers for Disease Control and Prevention's (CDC's) National Center for Health Statistics" (CIDRAP; see also: Vital Statistics Rapid Release [pdf]).

"India's pandemic death toll estimated at about 4 million: 10 times the official count" (NPR).

Virus Origins

"Will we ever find COVID-19's 'Patient Zero'? A lack of transparency on the virus' early days makes for an uphill battle" (Live Science).

"New data leads to rethinking (once more) where the pandemic actually began" (NPR; see also: Zenodo repository).

Public Health

"Public health officials have tools to beat back Covid again. Does anyone want to use them?" (STAT).

Opinion: "Confronting a legacy of scarcity: a plan for reinvesting in U.S. public health" (STAT).

Special Reports and Other Resources

GAO: COVID-19: Continued Attention Needed to Enhance Federal Preparedness, Response, Service Delivery, and Program Integrity (19 July 2021)

> "While COVID-19 cases have declined in recent months, the U.S. is still experiencing serious economic and public health repercussions due to the pandemic. In our 7th comprehensive report, we found more ways to improve federal programs related to the pandemic and other future emergencies. For example, we recommended that the CDC develop a plan to boost laboratory testing capacity, and that the IRS improve its communication on tax refund delays. This report makes 15 new recommendations. Agencies have agreed to implement most of our 72 previous recommendations on the COVID-19 response and have fully implemented 16."

Journal Articles

PLoS One: The Mean Unfulfilled Lifespan (MUL): A new indicator of the impact of mortality shocks on the individual lifespan, with application to mortality reversals induced by COVID-19 (27 July 2021)

> "Declines in period life expectancy at birth (PLEB) provide seemingly intuitive indicators of the impact of a cause of death on the individual lifespan. Derived under the assumption that future mortality conditions will remain indefinitely those observed during a reference period, however, their intuitive interpretation becomes problematic when period conditions reflect a temporary mortality "shock", resulting from a natural disaster or the diffusion of a new epidemic in the population for instance. Rather than to make assumptions about future mortality, I propose measuring the difference between a period average age at death and the average expected age at death of the same individuals (death cohort): the Mean Unfulfilled Lifespan (MUL). For fine-grained tracking of the mortality impact of an epidemic, I also provide an empirical shortcut to MUL estimation for small areas or short periods. For illustration, quarterly MUL values in 2020 are derived from estimates of COVID-19 deaths that might substantially underestimate overall mortality change in affected populations. These results nonetheless illustrate how MUL tracks the mortality impact of the pandemic in several national and sub-national populations. Using a seven-day rolling window, the empirical shortcut suggests MUL peaked at 6.43 years in Lombardy, 8.91 years in New Jersey, and 6.24 years in Mexico City for instance. Sensitivity analyses are presented, but in the case of COVID-19, the main uncertainty remains the potential gap between reported COVID-19 deaths and actual increases in the number of deaths induced by the pandemic in some of the most affected countries. Using actual number of deaths rather than reported COVID-19 deaths may increase seven-day MUL from

> 6.24 to 8.96 years in Mexico City and from 2.67 to 5.49 years in Lima for instance. In Guayas (Ecuador), MUL is estimated to have reached 12.7 years for the entire month of April 2020."

PNAS: Estimating SARS-CoV-2 infections from deaths, confirmed cases, tests, and random surveys (26 July 2021)

> "There are multiple sources of data giving information about the number of SARS-CoV-2 infections in the population, but all have major drawbacks, including biases and delayed reporting. For example, the number of confirmed cases largely underestimates the number of infections, and deaths lag infections substantially, while test positivity rates tend to greatly overestimate prevalence. Representative random prevalence surveys, the only putatively unbiased source, are sparse in time and space, and the results can come with big delays. Reliable estimates of population prevalence are necessary for understanding the spread of the virus and the effectiveness of mitigation strategies. We develop a simple Bayesian framework to estimate viral prevalence by combining several of the main available data sources. It is based on a discrete-time Susceptible–Infected–Removed (SIR) model with time-varying reproductive parameter. Our model includes likelihood components that incorporate data on deaths due to the virus, confirmed cases, and the number of tests administered on each day. We anchor our inference with data from random-sample testing surveys in Indiana and Ohio. We use the results from these two states to calibrate the model on positive test counts and proceed to estimate the infection fatality rate and the number of new infections on each day in each state in the United States. We estimate the extent to which reported COVID cases have underestimated true infection counts, which was large, especially in the first months of the pandemic. We explore the implications of our results for progress toward herd immunity."

SARS-CoV-2 Virus and Variants

News in Brief

"The lambda variant: what you should know and why experts say not to panic" (NPR).

"Patients with Alpha and Beta COVID-19 variants less likely to be asymptomatic, despite no increase in viral load" (Global Biodefense).

Long read: "How the coronavirus infects cells — and why Delta is so dangerous: Scientists are unpicking the life cycle of SARS-CoV-2 and how the virus uses tricks to evade detection" (Nature).

Journal Articles

NEJM: BNT162b2-Elicited Neutralization against New SARS-CoV-2 Spike Variants (29 July 2021)

> Letter to the editor: "Our results suggest that, as compared with the previously reported neutralization of B.1.1.7-spike, the additional E484K mutation, which is also found in the B.1.351 and B.1.526 lineages, caused little compromise to neutralization."

Clin Infect Dis: Impact of SARS-CoV-2 variant-associated RBD mutations on the susceptibility to serum antibodies elicited by COVID-19 infection or vaccination (26 July 2021)

> "Background: Several SARS-CoV-2 lineages with mutations at the spike protein receptor binding domain (RBD) have reduced susceptibility to antibody neutralization, and have been classified as Variants of Concern (VOCs) or Variants of Interest (VOIs). Here, we systematically compared the neutralization susceptibility and RBD binding of different VOCs/VOIs, including B.1.617.1 (kappa variant) and P.3 (theta variant) which were first detected in India and the Philippines, respectively.
>
> Methods: The neutralization susceptibility of the VOCs/VOIs (B.1.351, B.1.617.1 and P.3) and a non-VOC/VOI without RBD mutations (B.1.36.27) to convalescent sera from COVID-19 patients or BNT162b2 vaccinees was determined using a live virus microneutralization (MN) assay. Serum IgG binding to wild type and mutant RBDs were determined using an enzyme immunoassay.
>
> Results: The geometric mean neutralization titers (GMT) of B.1.351, P.3, and B.1.617.1 were significantly lower than that of B.1.36.27 for COVID-19 patients infected with non-VOCs/VOIs (3.4-5.7-fold lower) or individuals who have received 2 doses of BNT162b2 vaccine (4.4-7.3-fold lower). The GMT of B.1.351 or P.3 were lower than that of B.1.671.1. For the 4 patients infected with B.1.351 or B.1.617.1, the MN titer was highest for their respective lineage. RBD with E484K or E484Q mutation, either alone or in combination with other mutations, showed greatest reduction in serum IgG binding.
>
> Conclusion: P.3 and B.1.617.1 escape serum neutralization induced by natural infection or vaccine. Infection with one variant do not confer cross protection for heterologous lineages. Immunogenicity testing for second generation COVID-19 vaccines should include multiple variant and "non-variant" strains."

Clin Infect Dis: Neutralizing antibodies against SARS-CoV-2 variants induced by natural infection or vaccination: a systematic review and pooled meta-analysis (24 July 2021)

> "Recently emerged SARS-CoV-2 variants may pose a threat to immunity. A systematic landscape of neutralizing antibodies against emerging variants is needed. We systematically searched for studies that evaluated neutralizing antibodies titers induced by previous infection or vaccination against SARS-CoV-2 variants and collected individual data. We

> identified 106 studies meeting the eligibility criteria. Lineage B.1.351 (Beta), P.1 (Gamma) and B.1.617.2 (Delta) significantly escaped natural-infection-mediated neutralization, with an average of 4.1-fold (95% CI: 3.6-4.7), 1.8-fold (1.4-2.4), and 3.2-fold (2.4-4.1) reduction in live virus neutralization assay, while neutralizing titers against B.1.1.7 decreased slightly (1.4-fold, 95%CI: 1.2-1.6). Serum from vaccinees also led to significant reductions in neutralization of B.1.351 across different platforms, with an average of 7.1-fold (5.5-9.0) for non-replicating vector platform, 4.1-fold (3.7-4.4) for mRNA platform, and 2.5-fold (1.7-2.9) for protein subunit platform. Neutralizing antibodies levels induced by mRNA vaccines against SARS-CoV-2 variants were similar, or higher, than that derived from naturally-infected individuals."

NEJM: Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant (21 July 2021)

> "Background: The B.1.617.2 (delta) variant of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (Covid-19), has contributed to a surge in cases in India and has now been detected across the globe, including a notable increase in cases in the United Kingdom. The effectiveness of the BNT162b2 and ChAdOx1 nCoV-19 vaccines against this variant has been unclear.
>
> Methods: We used a test-negative case-control design to estimate the effectiveness of vaccination against symptomatic disease caused by the delta variant or the predominant strain (B.1.1.7, or alpha variant) over the period that the delta variant began circulating. Variants were identified with the use of sequencing and on the basis of the spike (S) gene status. Data on all symptomatic sequenced cases of Covid-19 in England were used to estimate the proportion of cases with either variant according to the patients' vaccination status.
>
> Results: Effectiveness after one dose of vaccine (BNT162b2 or ChAdOx1 nCoV-19) was notably lower among persons with the delta variant (30.7%; 95% confidence interval [CI], 25.2 to 35.7) than among those with the alpha variant (48.7%; 95% CI, 45.5 to 51.7); the results were similar for both vaccines. With the BNT162b2 vaccine, the effectiveness of two doses was 93.7% (95% CI, 91.6 to 95.3) among persons with the alpha variant and 88.0% (95% CI, 85.3 to 90.1) among those with the delta variant. With the ChAdOx1 nCoV-19 vaccine, the effectiveness of two doses was 74.5% (95% CI, 68.4 to 79.4) among persons with the alpha variant and 67.0% (95% CI, 61.3 to 71.8) among those with the delta variant.
>
> Conclusions: Only modest differences in vaccine effectiveness were noted with the delta variant as compared with the alpha variant after the receipt of two vaccine doses. Absolute differences in vaccine effectiveness were more marked after the receipt of the first dose. This finding would support efforts to maximize vaccine uptake with two doses among vulnerable populations."

Open Forum Infect Dis: Transmission of SARS-CoV-2 alpha variant (B.1.1.7) from a BNT162b2-vaccinated individual (20 July 2021)

> "Cases of SARS-CoV-2 acquisition after vaccination with BNT162b2 have been described but the risk of secondary transmission from fully-vaccinated individuals remains ill-defined. Herein we report a confirmed transmission of SARS-CoV-2 alpha variant (B.1.1.7) from a symptomatic immunocompetent woman 4 weeks after her second dose of BNT162b2, despite anti-spike seroconversion."

COVID-19 Vaccines

News in Brief

Approvals Ahead?

"FDA grants priority review to Pfizer/BioNTech Covid-19 vaccine; agency official says approval decision expected within two months" (CNN; see also: Pfizer statement [pdf]).

"AstraZeneca to seek US approval of COVID vaccine in 2nd half" (AP).

Effectiveness

"Efficacy of Pfizer/BioNTech Covid vaccine slips to 84% after six months, data show" (STAT; see also: medRxiv preprint).

"We're zeroing in on the 'holy grail' of COVID-19 immunity: There's no good way of measuring whether your vaccine worked—yet" (Atlantic).

The Variants

"Pfizer data suggest third dose of Covid-19 vaccine 'strongly' boosts protection against Delta variant" (CNN; see also: Pfizer earnings statement [pdf]).

"COVID vaccines slash viral spread – but Delta is an unknown: Studies show that vaccines reduce the spread of SARS-CoV-2 by more than 80%, but the Delta variant is creating fresh uncertainty" (Nature).

Vaccination Efforts

"Bhutan fully vaccinates 90 percent of eligible adults within a week" (WP).

"States are sitting on millions of surplus Covid-19 vaccine doses as expiration dates approach" (STAT).

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"Right now, protection against Covid-19 comes via an injection. But in future, those vaccines could come from inhalers or even pills" (BBC).

"Should children get COVID vaccines? What the science says: With vaccination campaigns underway in some countries while others weigh the options, Nature looks at the evidence for vaccinating younger people" (Nature).

"Vaccination in America might have only one tragic path forward: COVID-19 vaccination rates have fallen off a cliff. Will it take a deadly summer surge to change things?" (Atlantic).

Special Reports and Other Resources

TML: COVID-19 Vaccine Comparison Chart [pdf] (updated 23 July 2021)

Journal Articles

Response and Prevention

JAMA: Antibody Response After a Third Dose of the mRNA-1273 SARS-CoV-2 Vaccine in Kidney Transplant Recipients With Minimal Serologic Response to 2 Doses (23 July 2021)

> "This study examines the antibody responses to a third dose (100 µg) of the mRNA-1273 SARS-CoV-2 vaccine among kidney transplant recipients in France who had not responded to 2 doses of the vaccine….
>
> This study found that a third dose of mRNA-1273 vaccine induced a serologic response in 49% of kidney transplant recipients who did not respond after 2 doses. The findings in this large group of kidney transplant recipients are in accordance with other studies of solid organ transplant recipients. However, 51% of the patients did not develop anti–SARS-CoV-2 antibodies after the third dose, especially those receiving triple immunosuppression. The possibility that patients developed cellular immunity capable of conferring protection against severe disease was not assessed."

Clin Infect Dis: Prevention of COVID-19 by mRNA-based vaccines within the general population of California (20 July 2021)

> "Background: Estimates of COVID-19 vaccine effectiveness under real-world conditions, and understanding of barriers to uptake, are necessary to inform vaccine rollout.
>
> Methods: We enrolled cases (testing positive) and controls (testing negative) from among the population whose SARS-CoV-2 molecular diagnostic test results from 24 February-29 April 2021 were reported to the California Department of Public Health. Participants were matched on age, sex, and geographic region. We assessed participants' self-reported history

> of mRNA-based COVID-19 vaccine receipt (BNT162b2 and mRNA-1273). Participants were considered fully vaccinated two weeks after second dose receipt. Among unvaccinated participants, we assessed willingness to receive vaccination. We measured vaccine effectiveness (VE) via the matched odds ratio of prior vaccination, comparing cases with controls.
>
> Results: We enrolled 1023 eligible participants aged ≥18 years. Among 525 cases, 71 (13.5%) received BNT162b2 or mRNA-1273; 20 (3.8%) were fully vaccinated with either product. Among 498 controls, 185 (37.1%) received BNT162b2 or mRNA-1273; 86 (16.3%) were fully vaccinated with either product. Two weeks after second dose receipt, VE was 87.0% (95% confidence interval: 68.6-94.6%) and 86.2% (68.4-93.9%) for BNT162b2 and mRNA-1273, respectively. Fully vaccinated participants receiving either product experienced 91.3% (79.3-96.3%) and 68.3% (27.9-85.7%) VE against symptomatic and asymptomatic infection, respectively. Among unvaccinated participants, 42.4% (159/375) residing in rural regions and 23.8% (67/281) residing in urban regions reported hesitancy to receive COVID-19 vaccination.
>
> Conclusions: Authorized mRNA-based vaccines are effective at reducing documented SARS-CoV-2 infections within the general population of California. Vaccine hesitancy presents a barrier to reaching coverage levels needed for herd immunity."

Adverse Effects and Events

JAMA Dermatol: Association of Facial Pustular Neutrophilic Eruption With Messenger RNA–1273 SARS-CoV-2 Vaccine (28 July 2021)

> "This case report describes 2 patients with facial eruption that developed within 24 hours of receiving a first dose of a messenger RNA SARS-CoV-2 vaccine."

JAMA Oncol: Incidence of Axillary Adenopathy in Breast Imaging After COVID-19 Vaccination (22 July 2021)

> "This case series examines the incidence, timing, and characteristics of mammographic axillary adenopathy following COVID-19 vaccination….
>
> While the incidence of COVID-19 vaccine-induced adenopathy in our study appeared to be low at 3% compared with 16% of self-reported axillary swelling in previous COVID-19 vaccine trials, this incidence is still higher than axillary adenopathy in otherwise normal mammography, which was reported as 0.02% to 0.04%. Therefore, routine inquiring about recent history of COVID-19 vaccination is warranted. The incidence of adenopathy decreased over time with no adenopathy seen in patients who received the vaccine more

> than 28 days previously, which supports the recommendations from Society of Breast Imaging."

Vaccine: Patients with history of covid-19 had more side effects after the first dose of covid-19 vaccine (22 July 2021)

> "COVID-19 vaccination seems to be the most pertinent pharmacologic public health measure to control the pandemic. Reactogenicity symptoms were frequent in vaccine recipients mostly mild to moderate and commonly reported after the second dose. However, there is a lack of data in patients with a previous diagnosis of Covid-19.
>
> We analysed side effects of 311 patients after the first dose of Pfizer-BioNTech COVID-19 vaccine, in a french university hospital. We compared patients with COVID-19 history to naive individuals. All the data collected are based on self-reported, including COVID-19 exposure status.
>
> Overall, 229 (74%) patients reported at least one side effect. Among participants with history of Covid-19, 95% reported at least one adverse event versus 70% in naive patients ($p < 0.01$). However, symptom intensity was not different between the 2 groups.
>
> Vaccine recipients with prior COVID-19 reported more, but no more serious, side effects than naive participants."

JAMA Ophthalmol: Bilateral Acute Macular Neuroretinopathy After Vaccination Against SARS-CoV-2 (21 July 2021)

> "This case report describes bilateral acute macular neuroretinopathy in a woman who had just undergone COVID-19 vaccination."

JAMA: Sperm Parameters Before and After COVID-19 mRNA Vaccination (17 July 2021)

> "To address vaccine hesitancy based on concerns about fertility, this study assesses sperm parameters before and after mRNA vaccine administration….
>
> In this study of sperm parameters before and after 2 doses of a COVID-19 mRNA vaccine, there were no significant decreases in any sperm parameter among this small cohort of healthy men. Because the vaccines contain mRNA and not the live virus, it is unlikely that the vaccine would affect sperm parameters. While these results showed statistically significant increases in all sperm parameters, the magnitude of change is within normal individual variation and may be influenced by regression to the mean. Additionally, the increase may be due to the increased abstinence time before the second sample. Men with oligospermia did not experience further decline."

Safety and Effectiveness

JAMA Intern Med: Safety Evaluation of the Second Dose of Messenger RNA COVID-19 Vaccines in Patients With Immediate Reactions to the First Dose (26 July 2021)

> "This case series study examines the safety of second doses of messenger RNA COVID-19 vaccines after first-dose allergic reactions….
>
> Although mild symptoms were reported in 20% of patients with second dose administration, all patients who received a second dose safely completed their vaccination series and could use mRNA COVID-19 vaccines in the future when indicated. Second dose tolerance following reactions to the first dose argues that either many of these initial reactions are not all truly allergic reactions, or supports an allergic, but non–immunoglobulin E–mediated mechanism in which symptoms can typically be abated with premedications."

Lancet Infect Dis: Safety, tolerability, and immunogenicity of an aerosolised adenovirus type-5 vector-based COVID-19 vaccine (Ad5-nCoV) in adults: preliminary report of an open-label and randomised phase 1 clinical trial (26 July 2021)

> "SARS-CoV-2 has caused millions of deaths, and, since Aug 11, 2020, 20 intramuscular COVID-19 vaccines have been approved for use. We aimed to evaluate the safety and immunogenicity of an aerosolised adenovirus type-5 vector-based COVID-19 vaccine (Ad5-nCoV) in adults without COVID-19 from China.
>
> This was a randomised, single-centre, open-label, phase 1 trial done in Zhongnan Hospital (Wuhan, China), to evaluate the safety and immunogenicity of the Ad5-nCoV vaccine by aerosol inhalation in adults (≥18 years) seronegative for SARS-CoV-2. Breastfeeding or pregnant women and people with major chronic illnesses or history of allergies were excluded. Participants were enrolled and randomly assigned (1:1:1:1:1) into five groups to be vaccinated via intramuscular injection, aerosol inhalation, or both. Randomisation was stratified by sex and age (18–55 years or ≥56 years) using computer-generated randomisation sequences (block sizes of five). Only laboratory staff were masked to group assignment. The participants in the two aerosol groups received an initial high dose (2 × 1010 viral particles; HDmu group) or low dose (1 × 1010 viral particles; LDmu group) of Ad5-nCoV vaccine on day 0, followed by a booster on day 28. The mixed vaccination group received an initial intramuscular (5 × 1010 viral particles) vaccine on day 0, followed by an aerosolised booster (2 × 1010 viral particles) vaccine on day 28 (MIX group). The intramuscular groups received one dose (5 × 1010 viral particles; 1Dim group) or two doses (10 × 1010 viral particles; 2Dim group) of Ad5-nCoV on day 0. The primary safety outcome was adverse events 7 days after each vaccination, and the primary immunogenicity outcome was anti-SARS-CoV-2 spike receptor IgG antibody and SARS-CoV-2 neutralising

antibody geometric mean titres at day 28 after last vaccination. This trial is registered with ClinicalTrials.gov, number NCT04552366.

Between Sept 28, 2020, and Sept 30, 2020, 230 individuals were screened for inclusion, of whom 130 (56%) participants were enrolled into the trial and randomly assigned into one of the five groups (26 participants per group). Within 7 days after vaccination, adverse events occurred in 18 (69%) in the HDmu group, 19 (73%) in the LDmu group, 19 (73%) in the MIX group, 19 (73%) in the 1Dim group, and 15 (58%) in the 2Dim group. The most common adverse events reported 7 days after the first or booster vaccine were fever (62 [48%] of 130 participants), fatigue (40 [31%] participants), and headache (46 [35%] participants). More adverse events were reported in participants who received intramuscular vaccination, including participants in the MIX group (49 [63%] of 78 participants), than those who received aerosol vaccine (13 [25%] of 52 participants) after the first vaccine vaccination. No serious adverse events were noted within 56 days after the first vaccine. At days 28 after last vaccination, geometric mean titres of SARS-CoV-2 neutralising antibody was 107 (95% CI 47–245) in the HDmu group, 105 (47–232) in the LDmu group, 396 (207–758) in the MIX group, 95 (61–147) in the 1Dim group, and 180 (113–288) in the 2Dim group. The geometric mean concentrations of receptor binding domain-binding IgG was 261 EU/mL (95% CI 121–563) in the HDmu group, 289 EU/mL (138–606) in the LDmu group, 2013 EU/mL (1180–3435) in the MIX group, 915 EU/mL (588–1423) in the 1Dim group, and 1190 EU/mL (776–1824) in the 2Dim group.

Aerosolised Ad5-nCoV is well tolerated, and two doses of aerosolised Ad5-nCoV elicited neutralising antibody responses, similar to one dose of intramuscular injection. An aerosolised booster vaccination at 28 days after first intramuscular injection induced strong IgG and neutralising antibody responses. The efficacy and cost-effectiveness of aerosol vaccination should be evaluated in future studies."

Ann Intern Med: SARS-CoV-2 Vaccine Effectiveness in a High-Risk National Population in a Real-World Setting (20 July 2021)

"Background: With the emergency use authorization of multiple vaccines against SARS-CoV-2 infection, data are urgently needed to determine their effectiveness in a real-world setting.

Objective: To evaluate the short-term effectiveness of vaccines in preventing SARS-CoV-2 infection.

Design: Test-negative case-control study using conditional logistic regression.

Setting: U.S. Department of Veterans Affairs health care system.

Participants: All veterans who had testing for SARS-CoV-2 infection between 15 December 2020 and 4 March 2021 and no confirmed infection before 15 December 2020.

> Intervention: SARS-CoV-2 vaccination with either the BNT-162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna) vaccine as part of routine clinical care.
>
> Measurements: Effectiveness of vaccination against confirmed SARS-CoV-2 infection.
>
> Results: Among 54 360 persons who tested positive and 54 360 propensity score-matched control participants, the median age was 61 years, 83.6% were male, and 62% were White. Median body mass index was 31 kg/m2 among those who tested positive and 30 kg/m2 among those who tested negative. Among those who tested positive, 9800 (18.0%) had been vaccinated; among those who tested negative, 17 825 (32.8%) had been vaccinated. Overall vaccine effectiveness 7 or more days after the second dose was 97.1% (95% CI, 96.6% to 97.5%). Effectiveness was 96.2% (CI, 95.5% to 96.9%) for the Pfizer-BioNTech BNT-162b2 vaccine and 98.2% (CI, 97.5% to 98.6%) for the Moderna mRNA-1273 vaccine. Effectiveness remained above 95% regardless of age group, sex, race, or presence of comorbidities.
>
> Limitations: Predominantly male population; lack of data on disease severity, mortality, and effectiveness by SARS-CoV-2 variants of concern; and short-term follow-up.
>
> Conclusion: Currently used vaccines against SARS-CoV-2 infection are highly effective in preventing confirmed infection in a high-risk population in a real-world setting."

Vaccine Hesitancy, Vaccine Denial, and Health Misinformation

News in Brief

"America is getting unvaccinated people all wrong: They're not all anti-vaxxers, and treating them as such is making things worse" (Atlantic).

Vaccine Refusal/Denial

"My community refuses to get vaccinated. Now Delta is here. Only 35 percent of Arkansas is fully vaccinated, and with case rates rising, living there can feel like moving through a distorted reality" (Atlantic).

"'I'm sorry, but it's too late': Alabama doctor on treating unvaccinated, dying COVID patients" (AL.com).

Misinformation

"The life cycle of a COVID-19 vaccine lie" (NPR).

President Biden said social media platforms like Facebook are killing people by allowing COVID-19 vaccine misinformation on their services (CNBC).

"Democrats want to hold social media companies responsible for health misinformation" (NPR).

Long read: "Facebook and YouTube spent a year fighting covid misinformation. It's still spreading: The social media giants have struggled to find and take down anti-vaccine propaganda. But medical misinformation has thrived on their platforms for years" (WP).

Special Reports and Other Resources

ISD: Disinformation Overdose: A study of the Crisis of Trust among Vaccine Sceptics and Anti-Vaxxers (06 July 2021)

> Report originally published in German; updated with English translation.
>
> "The issue of public health measures has become a gateway and incubator for conspiracy theorists, far-right extremists and anti-vaxxers. This report by ISD Germany provides for the first time a comprehensive insight into the online networks of the vaccine-sceptic scene in Germany. Over 400,000 posts from more than 1,000 users on Facebook, Twitter, Instagram and Telegram were collected in the period from 21 December 2020 to 5 April 2021. In addition, 14 experts from the health sector as well as from science, education and public communication were interviewed on the topic of vaccination scepticism and vaccine-related disinformation. The key insight is clear: the targeted influencing of the public vaccination debate is successful in parts of the population. The positions of anti-vaxxers, which are often based on disinformation, are increasingly normalised.
>
> On Telegram, the readership of various channels increased by up to 471%. Relevant Facebook pages also saw an average growth of 21% to a total of over 4.5 million followers between April 2020 and April 2021; a development that could also be observed on other platforms. This growth goes hand in hand with the constant networking of the leading heads of the scenes, from 'Querdenker' (eng. 'lateral thinkers') to far-right extremists, who reference each other on their platforms and thus create an illusion of scientificity. While ideological diversity exists within this network, the boundaries to general conspiracy myths and extremist ideologies are fluid. In terms of content, clearly distinguishable narratives emerge. They are used to achieve the greatest possible loss of trust in vaccines and health policies. Particularly prevalent are narratives on 'vaccine deaths', 'vaccine health damage', on the vaccine by AstraZeneca, on 'compulsory vaccination', on discrediting experts and on conspiracy myths. In the medium term, disinformation and mistrust endanger both political decision-making and rational decision-making. In the short term, vaccination efforts and further measures to combat the pandemic are made considerably more difficult."

Journal Articles

Clin Infect Dis: Deliberation, Dissent, and Distrust: Understanding distinct drivers of COVID-19 vaccine hesitancy in the United States (16 July 2021)

> "Background: Despite the availability of safe and efficacious COVID-19 vaccines, a significant proportion of the American public remains unvaccinated and does not appear immediately interested in receiving the vaccine.
>
> Methods: In this study, we analyzed data from the U.S. Census Bureau's Household Pulse Survey, a biweekly cross-sectional survey of U.S. households. We estimated the prevalence of vaccine hesitancy across states and nationally and assessed the predictors of vaccine hesitancy and vaccine rejection. Additionally, we examined the underlying reasons for vaccine hesitancy, grouped into thematic categories.
>
> Results: A total of 459,235 participants were surveyed from January 6 to March 29, 2021. While vaccine uptake increased from 7.7 to 47 percent, vaccine hesitancy rates remained relatively fixed: overall, 10.2 percent reported that they would probably not get a vaccine, and 8.2 percent would definitely not get a vaccine. Income, education, and state political leaning strongly predicted vaccine hesitancy. However, while both female sex and Black race were factors predicting hesitancy, among those who were hesitant, these same characteristics predicted vaccine reluctance rather than rejection. Those who expressed reluctance invoked mostly "deliberative" reasons while those who rejected the vaccine were also likely to invoke reasons of "dissent" and "distrust".
>
> Conclusion: Vaccine hesitancy comprises a sizable proportion of the population and is large enough to threaten achieving herd immunity. Distinct subgroups of hesitancy have distinctive socio-demographic associations as well as cognitive and affective predilections. Segmented public health solutions are needed to target interventions and optimize vaccine uptake."

Nat Med: COVID-19 vaccine acceptance and hesitancy in low- and middle-income countries (16 July 2021)

> "Widespread acceptance of COVID-19 vaccines is crucial for achieving sufficient immunization coverage to end the global pandemic, yet few studies have investigated COVID-19 vaccination attitudes in lower-income countries, where large-scale vaccination is just beginning. We analyze COVID-19 vaccine acceptance across 15 survey samples covering 10 low- and middle-income countries (LMICs) in Asia, Africa and South America, Russia (an upper-middle-income country) and the United States, including a total of 44,260 individuals. We find considerably higher willingness to take a COVID-19 vaccine in our LMIC samples (mean 80.3%; median 78%; range 30.1 percentage points) compared with the United States (mean 64.6%) and Russia (mean 30.4%). Vaccine acceptance in LMICs is primarily explained

> by an interest in personal protection against COVID-19, while concern about side effects is the most common reason for hesitancy. Health workers are the most trusted sources of guidance about COVID-19 vaccines. Evidence from this sample of LMICs suggests that prioritizing vaccine distribution to the Global South should yield high returns in advancing global immunization coverage. Vaccination campaigns should focus on translating the high levels of stated acceptance into actual uptake. Messages highlighting vaccine efficacy and safety, delivered by healthcare workers, could be effective for addressing any remaining hesitancy in the analyzed LMICs."

Breakthrough Infections, Reinfections, and Coinfections

Journal Articles

NEJM: Covid-19 Breakthrough Infections in Vaccinated Health Care Workers (28 July 2021)

> "Background: Despite the high efficacy of the BNT162b2 messenger RNA vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), rare breakthrough infections have been reported, including infections among health care workers. Data are needed to characterize these infections and define correlates of breakthrough and infectivity.
>
> Methods: At the largest medical center in Israel, we identified breakthrough infections by performing extensive evaluations of health care workers who were symptomatic (including mild symptoms) or had known infection exposure. These evaluations included epidemiologic investigations, repeat reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assays, antigen-detecting rapid diagnostic testing (Ag-RDT), serologic assays, and genomic sequencing. Correlates of breakthrough infection were assessed in a case-control analysis. We matched patients with breakthrough infection who had antibody titers obtained within a week before SARS-CoV-2 detection (peri-infection period) with four to five uninfected controls and used generalized estimating equations to predict the geometric mean titers among cases and controls and the ratio between the titers in the two groups. We also assessed the correlation between neutralizing antibody titers and N gene cycle threshold (Ct) values with respect to infectivity.
>
> Results: Among 1497 fully vaccinated health care workers for whom RT-PCR data were available, 39 SARS-CoV-2 breakthrough infections were documented. Neutralizing antibody titers in case patients during the peri-infection period were lower than those in matched uninfected controls (case-to-control ratio, 0.361; 95% confidence interval, 0.165 to 0.787). Higher peri-infection neutralizing antibody titers were associated with lower infectivity (higher Ct values). Most breakthrough cases were mild or asymptomatic, although 19% had

> persistent symptoms (>6 weeks). The B.1.1.7 (alpha) variant was found in 85% of samples tested. A total of 74% of case patients had a high viral load (Ct value, <30) at some point during their infection; however, of these patients, only 17 (59%) had a positive result on concurrent Ag-RDT. No secondary infections were documented.
>
> Conclusions: Among fully vaccinated health care workers, the occurrence of breakthrough infections with SARS-CoV-2 was correlated with neutralizing antibody titers during the peri-infection period. Most breakthrough infections were mild or asymptomatic, although persistent symptoms did occur."

Infect Control Hosp Epidemiol: Risk Factors and Outcomes Associated with Community-Onset and Hospital-Acquired Co-infection in Patients Hospitalized for COVID-19: A Multi-Hospital Cohort Study (26 July 2021)

> "Background: We sought to determine the incidence of community-onset and hospital-acquired co-infection in patients hospitalized with COVID-19 and evaluate associated predictors and outcomes.
>
> Methods: Multicenter retrospective cohort study of patients hospitalized for COVID-19, 3/2020 to 8/2020, across 38 Michigan hospitals assessed for prevalence, predictors, and outcomes of community-onset or hospital-acquired co-infection. In-hospital and 60-day mortality, readmission, discharge to long-term care facility (LTCF), and mechanical ventilation duration, were assessed for patients with vs. without co-infection.
>
> Results: Of 2205 patients with COVID-19, 6.4% (N=141) had a co-infection (3.0% community-onset, 3.4% hospital-acquired). 64.9% of patients without co-infection received antibiotics. Community-onset co-infection predictors include admission from LTCF (OR 3.98, 95% CI 2.34-6.76, p<0.001) and admission to intensive care (OR 4.34, 95% CI 2.87-6.55, p<0.001). Hospital-acquired co-infection predictors include fever (OR 2.46, 95% CI 1.15-5.27, p=0.02) and advanced respiratory support (OR 40.72, 95% CI 13.49-122.93, p<0.001). Patients with (vs. without) community-onset co-infection had longer mechanical ventilation (OR 3.31, 95% CI 1.67-6.56, p=0.001) and higher in-hospital (OR 1.90, 95% CI 1.06-3.40 p=0.03) and 60-day mortality (OR 1.86, 95% CI 1.05-3.29 p=0.03). Patients with (vs. without) hospital-acquired co-infection had higher discharge to LTCF (OR 8.48, 95%CI 3.30-21.76 p<0.001), in-hospital (OR 4.17, 95% CI 2.37-7.33, p=<.001) and 60-day mortality (OR 3.66, 95% CI 2.11-6.33, p=<.001).
>
> Conclusion: Despite community-onset and hospital-acquired co-infection being uncommon, most patients hospitalized with COVID-19 received antibiotics. Admission from LTCF and to ICU were associated with increased risk of community-onset co-infection. Future work should prospectively validate predictors of COVID-19 co-infection to facilitate antibiotic reduction."

Emerg Infect Dis: Breakthrough Infections of SARS-CoV-2 Gamma Variant in Fully Vaccinated Gold Miners, French Guiana, 2021 (21 July 2021)

> "An outbreak of severe acute respiratory syndrome coronavirus 2 caused by the Gamma variant of concern infected 24/44 (55%) employees of a gold mine in French Guiana (87% symptomatic, no severe forms). The attack rate was 60% (15/25) among fully vaccinated miners and 75% (3/4) among unvaccinated miners without a history of infection."

Treatments and Management

News in Brief

The FDA revised the emergency use authorization labeling for baricitinib – it is no longer required that it is used in combination with remdesivir (FDA [pdf]).

A widely-cited (including 2 recent meta-analyses) Egyptian study of ivermectin for COVID-19 patients has been retracted over concerns of plagiarism and issues with their data (Guardian).

Long read: "'There is a real cost': As Covid shows, barring bedside visitors from ICU deprives patients of the best care" (STAT).

Special Reports and Other Resources

TML: Treatments Considered for COVID-19 [pdf] (updated 23 July 2021)

Journal Articles

NEJM: Tofacitinib in Patients Hospitalized with Covid-19 Pneumonia (29 July 2021)

> "Background: The efficacy and safety of tofacitinib, a Janus kinase inhibitor, in patients who are hospitalized with coronavirus disease 2019 (Covid-19) pneumonia are unclear.
>
> Methods: We randomly assigned, in a 1:1 ratio, hospitalized adults with Covid-19 pneumonia to receive either tofacitinib at a dose of 10 mg or placebo twice daily for up to 14 days or until hospital discharge. The primary outcome was the occurrence of death or respiratory failure through day 28 as assessed with the use of an eight-level ordinal scale (with scores ranging from 1 to 8 and higher scores indicating a worse condition). All-cause mortality and safety were also assessed.

> Results: A total of 289 patients underwent randomization at 15 sites in Brazil. Overall, 89.3% of the patients received glucocorticoids during hospitalization. The cumulative incidence of death or respiratory failure through day 28 was 18.1% in the tofacitinib group and 29.0% in the placebo group (risk ratio, 0.63; 95% confidence interval [CI], 0.41 to 0.97; P = 0.04). Death from any cause through day 28 occurred in 2.8% of the patients in the tofacitinib group and in 5.5% of those in the placebo group (hazard ratio, 0.49; 95% CI, 0.15 to 1.63). The proportional odds of having a worse score on the eight-level ordinal scale with tofacitinib, as compared with placebo, was 0.60 (95% CI, 0.36 to 1.00) at day 14 and 0.54 (95% CI, 0.27 to 1.06) at day 28. Serious adverse events occurred in 20 patients (14.1%) in the tofacitinib group and in 17 (12.0%) in the placebo group.
>
> Conclusions: Among patients hospitalized with Covid-19 pneumonia, tofacitinib led to a lower risk of death or respiratory failure through day 28 than placebo."

Emerg Infect Dis: Emergence of SARS-COV-2 Spike Protein Escape Mutation Q493R after Treatment for COVID-19 (27 July 2021)

> "We report in vivo selection of a severe acute respiratory syndrome coronavirus 2 spike mutation (Q493R) conferring simultaneous resistance to bamlanivimab and etesivimab. This mutation was isolated from a patient who had coronavirus disease and was treated with these drugs."

JAMA: Effect of Canakinumab vs Placebo on Survival Without Invasive Mechanical Ventilation in Patients Hospitalized With Severe COVID-19 (20 July 2021)

> "Question Is the anti–interleukin-1β antibody canakinumab effective to treat patients hospitalized with COVID-19 and hyperinflammation?
>
> Finding This randomized clinical trial included 454 patients hospitalized with severe COVID-19 not requiring invasive mechanical ventilation (IMV) and with elevated C-reactive protein or ferritin levels. Treatment with intravenous canakinumab vs placebo resulted in survival without IMV at 29 days of 88.8% vs 85.7%, a difference that was not statistically significant.
>
> Meaning Among patients hospitalized with severe COVID-19, treatment with canakinumab, compared with placebo, did not significantly increase the likelihood of survival without IMV."

J Infect Dis: Real-World Clinical Outcomes of Bamlanivimab and Casirivimab-Imdevimab among High-Risk Patients with Mild to Moderate Coronavirus Disease 2019 (19 July 2021)

> "Background: Bamlanivimab and casirivimab-imdevimab are authorized for treatment of high-risk patients with mild to moderate coronavirus disease-2019 (COVID-19). We compared the outcomes of patients who received these therapies to identify factors associated with hospitalization and other clinical outcomes.

> Methods: Adult patients who received monoclonal antibody from November 19, 2020 to February 11, 2021 were selected and divided into those who received bamlanivimab (n=2747) and casirivimab-imdevimab (n=849). The 28-day all-cause and COVID-19-related hospitalizations were compared between the groups.
>
> Results: The population included 3596 patients; median age was 62 years; and 50% were female. All had ≥1 medical comorbidity; 55% had multiple comorbidities. All cause- and COVID-19-related hospitalization rates at 28 days were 3.98% and 2.56%, respectively. After adjusting for medical comorbidities, there was no significant difference in all cause- and COVID-19-related hospitalization rates between bamlanivimab and casirivimab-imdevimab (adjusted HR, 1.4, 95% CI 0.9-2.2 and 1.6, 95% CI 0.8-2.7, respectively). Chronic kidney, respiratory and cardiovascular diseases, and immunocompromised status were associated with higher likelihood of hospitalization.
>
> Conclusion: This observational study on the use of bamlanivimab and casirivimab-imdevimab in high-risk patients showed similarly low rates of hospitalization. The number and type of medical comorbidities are associated with hospitalizations after monoclonal antibody treatment."

JAMA: Effect of Oral Azithromycin vs Placebo on COVID-19 Symptoms in Outpatients With SARS-CoV-2 Infection: A Randomized Clinical Trial (16 July 2021)

> "Question Does a single oral dose of azithromycin lead to absence of symptoms at day 14 in outpatients with COVID-19 compared with placebo?
>
> Findings In this randomized trial that included 263 participants with SARS-CoV-2 infection, treatment with a single oral dose of azithromycin, 1.2 g, vs placebo resulted in self-reported absence of COVID-19 symptoms at day 14 in 50% vs 50%; this was not statistically significant.
>
> Meaning Among outpatients with SARS-CoV-2 infection, treatment with a single dose of oral azithromycin compared with placebo did not result in a greater likelihood of being free of symptoms at day 14."

JAMA Netw Open: Association of Remdesivir Treatment With Survival and Length of Hospital Stay Among US Veterans Hospitalized With COVID-19 (15 July 2021)

> "Question Is remdesivir treatment associated with improved survival or shortened hospitalizations among people with COVID-19 in routine care settings?
>
> Findings In this cohort study of 2344 US veterans hospitalized with COVID-19, remdesivir therapy was not associated with improved 30-day survival but was associated with a significant increase in median time to hospital discharge.

> Meaning The findings suggest that routine use of remdesivir may be associated with increased use of hospital beds but not with improvements in survival."

Pre-Existing Conditions, Comorbidities, and Impact on Other Diseases

News in Brief

"WHO warns that HIV infection increases risk of severe and critical COVID-19" (WHO; see also: full report [pdf]).

Journal Articles

JAMA Oncol: Assessment of Prostate Cancer Treatment Among Black and White Patients During the COVID-19 Pandemic (22 July 2021)

> "Question Was the association of the COVID-19 pandemic with cancer surgery similar for Black and White patients with prostate cancer?
>
> Findings In this multi-institutional cohort study of patients with untreated nonmetastatic prostate cancer during the initial COVID-19 lockdown, only 1% of Black men underwent prostatectomy, while 26% of White patients did. Prior to the pandemic, there was no difference in the rate of prostatectomy between the 2 races (18% of Black men and 19% of White men).
>
> Meaning This study suggests that during the initial phase of the COVID-19 pandemic, hospital restrictions were unbalanced, and Black patients experienced a disproportionate lower rate of prostatectomies."

Sci Rep: Long-term effects of malnutrition on severity of COVID-19 (22 July 2021)

> "The COVID-19 pandemic is a public health crisis that has the potential to exacerbate worldwide malnutrition. This study examines whether patients with a history of malnutrition are predisposed to severe COVID-19. To do so, data on 103,099 COVID-19 inpatient encounters from 56 hospitals in the United States between March 2020 and June 2020 were retrieved from the Cerner COVID-19 Dataset. Patients with a history of malnutrition between 2015 and 2019 were identified, and a random intercept logistic regression models for pediatric and adult patients were built controlling for patient demographics, socioeconomic status, admission vital signs, and related comorbidities. Statistical interactions between malnutrition and patient age were significant in both the pediatric [log-odds and 95% confidence interval: 0.094 (0.012, 0.175)] and adult [− 0.014

> (− 0.021, − 0.006] models. These interactions, together with the main effect terms of malnutrition and age, imply higher odds for severe COVID-19 for children between 6 and 17 years with history of malnutrition. Even higher odds of severe COVID-19 exist for adults (with history of malnutrition) between 18 and 79 years. These results indicate that the long-term effect of malnutrition predisposes patients to severe COVID-19 in an age-dependent way."

PLoS One: Relation of prior statin and anti-hypertensive use to severity of disease among patients hospitalized with COVID-19: Findings from the American Heart Association's COVID-19 Cardiovascular Disease Registry (15 July 2021)

> "Background: Statins have anti-inflammatory and immunomodulatory effects that may reduce the severity of coronavirus disease 2019 (COVID-19), in which organ dysfunction is mediated by severe inflammation. Large studies with diverse populations evaluating statin use and outcomes in COVID-19 are lacking.
>
> Methods and results: We used data from 10,541 patients hospitalized with COVID-19 through September 2020 at 104 US hospitals enrolled in the American Heart Association's COVID-19 Cardiovascular Disease (CVD) Registry to evaluate the associations between statin use and outcomes. Prior to admission, 42% of subjects (n = 4,449) used statins (7% on statins alone, 35% on statins plus anti-hypertensives). Death (or discharge to hospice) occurred in 2,212 subjects (21%). Outpatient use of statins, either alone or with anti-hypertensives, was associated with a reduced risk of death (adjusted odds ratio [aOR] 0.59, 95% CI 0.50-0.69), adjusting for demographic characteristics, insurance status, hospital site, and concurrent medications by logistic regression. In propensity-matched analyses, use of statins and/or anti-hypertensives was associated with a reduced risk of death among those with a history of CVD and/or hypertension (aOR 0.68, 95% CI 0.58-0.81). An observed 16% reduction in odds of death among those without CVD and/or hypertension was not statistically significant.
>
> Conclusions: Patients taking statins prior to hospitalization for COVID-19 had substantially lower odds of death, primarily among individuals with a history of CVD and/or hypertension. These observations support the continuation and aggressive initiation of statin and anti-hypertensive therapies among patients at risk for COVID-19, if these treatments are indicated based upon underlying medical conditions."

Ann Intern Med: Sickle Cell Disorders and Severe COVID-19 Outcomes: A Cohort Study (20 July 2021)

> Research letter – "Objective: To evaluate the risks for COVID-19–related hospitalization and death in children and adults with sickle cell disorders (disease and trait, separately) using a population-level database of linked electronic health care records….

> Our analysis estimated a 4-fold increased risk for COVID-19–related hospitalization and a 2.6-fold increased risk for COVID-19–related death for sickle cell disease. Sickle cell trait was also associated with increased risks for both outcomes, albeit to a lesser extent. Several aspects of sickle cell phenotypes overlap with the pathophysiology of severe COVID-19, which could be relevant mechanisms worthy of further study, as should the directionality of infection and sickle crisis."

Long COVID / Post-COVID Period

News in Brief

"Doctors worry that memory problems after COVID-19 may set the stage for Alzheimer's" (NPR).

"How COVID-19 long haulers could change the U.S. disability benefits system" (Time).

Long read: "COVID-19 long haulers: With the risks of drug development prohibitive, repurposed or repositioned medicines appear the best hope against long-COVID, a condition that still raises many unanswered questions" (Nat Biotechnol).

Journal Articles

JAMA Netw Open: Self-reported Memory Problems 8 Months After COVID-19 Infection (29 July 2021)

"This cohort study examines self-reported memory problems 8 months after COVID-19 infection….

We examined the prevalence of self-reported memory problems in a large group of COVID-19 patients who were not hospitalized and had a relatively mild disease. Eight months after the positive SARS-CoV-2 test, the prevalence of memory problems in this group was higher than in the control group with a negative test or in the untested control population.

Most of the SARS-CoV-2–positive participants with memory problems also reported a worsening of their health compared with 1 year prior. Our findings suggest that SARS-CoV-2 may negatively impact memory even 8 months after having a mild case of the disease, and this can be associated with a worsening of health and PASC. The findings are a strong impetus to reconsider the notion that COVID-19 can be a mild disease. It also questions whether the current home-treatment strategies are optimal for the long-term outcome. Our results suggest that memory problems may be a part of PASC, but firmer conclusions should await a longer follow-up period."

Infection: Long COVID, a comprehensive systematic scoping review (28 July 2021)

> "Purpose: To find out what is known from literature about Long COVID until January 30, 2021.
>
> Methods: We undertook a four-step search with no language restriction. A preliminary search was made to identify the keywords. A search strategy of all electronic databases resulted in 66 eligible studies. A forward and backward search of the references and citations resulted in additional 54 publications. Non-English language articles were translated using Google Translate. We conducted our scoping review based on the PRISMA-ScR Checklist.
>
> Results: Of 120 papers, we found only one randomized clinical trial. Of the 67 original studies, 22 were cohort, and 28 were cross-sectional studies. Of the total 120 publications, 49.1% focused on signs and symptoms, 23.3% on management, and 10.8% on pathophysiology. Ten publications focused on imaging studies. The results are also presented extensively in a narrative synthesis in separated sections (nomenclature, diagnosis, pathophysiology, risk factors, signs/symptoms, management).
>
> Conclusions: The controversies in its definition have impaired proper recognition and management. The predominant symptoms were: fatigue, breathlessness, arthralgia, sleep difficulties, and chest pain. Recent reports also point to the risk of long-term sequela with cutaneous, respiratory, cardiovascular, musculoskeletal, mental health, neurologic, and renal involvement in those who survive the acute phase of the illness."

Open Forum Infect Dis: Post-acute sequelae of SARS-CoV-2 infection and impact on quality of life 1-6 months after illness and association with initial symptom severity (27 July 2021)

> "Background: Individuals with coronavirus disease 2019 (COVID-19) may have persistent symptoms following their acute illness. The prevalence and predictors of these symptoms, termed post-acute sequelae of SARS-CoV-2 (PASC), are not fully described.
>
> Methods: Participants discharged from an outpatient telemedicine program for COVID-19 were emailed a survey (1-6 months after discharge) about ongoing symptoms, acute illness severity, and quality of life. Standardized telemedicine notes from acute illness were used for covariates (comorbidities and provider-assessed symptom severity). Bivariate and multivariable analyses were performed to assess predictors of persistent symptoms.
>
> Results: Two hundred and ninety patients completed the survey, of whom 115 (39.7%) reported persistent symptoms including fatigue (n= 59, 20.3%), dyspnea on exertion (n=41, 14.1%), and mental fog (n=39, 13.5%) among others. Proportion of persistent symptoms did

not differ based on duration since illness (<90 days: n=32, 37.2% versus >90 days: n=80, 40.4%, p = 0.61). Predictors of persistent symptoms included provider-assessed moderate-severe illness (aOR 3.24, 95% CI 1.75, 6.02), female sex (aOR 1.99 95% 0.98, 4.04; >90 days out: aOR 2.24 95% CI 1.01, 4.95), and middle age (aOR 2.08 95% CI 1.07, 4.03). Common symptoms associated with reports of worse physical health included weakness, fatigue, myalgias, and mental fog.

Conclusions: Symptoms following acute COVID-19 are common and may be predicted by factors during the acute phase of illness. Fatigue and neuropsychiatric symptoms figured prominently. Select symptoms seem to be particularly associated with perceptions of physical health following COVID-19 and warrant specific attention on future studies of PASC."

J R Soc Med: Symptoms, complications and management of long COVID: a review (15 July 2021)

"Globally, there are now over 160 million confirmed cases of COVID-19 and more than 3 million deaths. While the majority of infected individuals recover, a significant proportion continue to experience symptoms and complications after their acute illness. Patients with 'long COVID' experience a wide range of physical and mental/psychological symptoms. Pooled prevalence data showed the 10 most prevalent reported symptoms were fatigue, shortness of breath, muscle pain, joint pain, headache, cough, chest pain, altered smell, altered taste and diarrhoea. Other common symptoms were cognitive impairment, memory loss, anxiety and sleep disorders. Beyond symptoms and complications, people with long COVID often reported impaired quality of life, mental health and employment issues. These individuals may require multidisciplinary care involving the long-term monitoring of symptoms, to identify potential complications, physical rehabilitation, mental health and social services support. Resilient healthcare systems are needed to ensure efficient and effective responses to future health challenges."

PLoS One: Burden of post-COVID-19 syndrome and implications for healthcare service planning: A population-based cohort study (12 July 2021)

"Background: Longer-term consequences after SARS-CoV-2 infection are becoming an important burden to societies and healthcare systems. Data on post-COVID-19 syndrome in the general population are required for the timely planning of healthcare services and resources. The objective of this study was to assess the prevalence of impaired health status and physical and mental health symptoms among individuals at least six months after SARS-CoV-2 infection, and to characterize their healthcare utilization.

Methods: This population-based prospective cohort study (Zurich SARS-CoV-2 Cohort) enrolled 431 adults from the general population with polymerase chain reaction-confirmed SARS-CoV-2 infection reported to health authorities between 27 February 2020 and 05 August 2020 in the Canton of Zurich, Switzerland. We evaluated the proportion of

> individuals reporting not to have fully recovered since SARS-CoV-2 infection, and the proportion reporting fatigue (Fatigue Assessment Scale), dyspnea (mMRC dyspnea scale) or depression (DASS-21) at six to eight months after diagnosis. Furthermore, the proportion of individuals with at least one healthcare contact after their acute illness was evaluated. Multivariable logistic regression models were used to assess factors associated with these main outcomes.
>
> Results: Symptoms were present in 385 (89%) participants at diagnosis and 81 (19%) were initially hospitalized. At six to eight months, 111 (26%) reported not having fully recovered. 233 (55%) participants reported symptoms of fatigue, 96 (25%) had at least grade 1 dyspnea, and 111 (26%) had DASS-21 scores indicating symptoms of depression. 170 (40%) participants reported at least one general practitioner visit related to COVID-19 after acute illness, and 10% (8/81) of initially hospitalized individuals were rehospitalized. Individuals that have not fully recovered or suffer from fatigue, dyspnea or depression were more likely to have further healthcare contacts. However, a third of individuals (37/111) that have not fully recovered did not seek further care.
>
> Conclusions: In this population-based study, a relevant proportion of participants suffered from longer-term consequences after SARS-CoV-2 infection. With millions infected across the world, our findings emphasize the need for the timely planning of resources and patient-centered services for post-COVID-19 care."

Women's Health, Pregnancy, and Perinatal Care

Journal Articles

Ultrasound Obstet Gynecol: Short-term outcome of pregnant women vaccinated by BNT162b2 mRNA COVID-19 vaccine (01 July 2021)

> "Objective: To determine the immunogenicity and reactogenicity of Pfizer's BNT162b2 COVID-19 vaccine among pregnant women compared with non-pregnant women, and to evaluate the obstetric outcome following vaccination.
>
> Methods: An observational case-control study of pregnant women, who were vaccinated by a 2-dose regimen of BNT162b2 vaccine during gestation between January-February 2021 (study group) and were compared to age-matched non-pregnant women who received the vaccine during the same time period (control group). Participants received a digital questionnaire 1-4 weeks after the second dose and were asked to provide information regarding demographics, medications, medical history, history of prior SARS-CoV-2 infection, timing of COVID-19 vaccine doses, and side effects after each vaccine dose. A

> second digital questionnaire, regarding current pregnancy and delivery outcomes was sent to patients of the study group after the calculated due date. All recruited patients were offered a serology blood test for SARS-CoV-2 IgG following the second vaccination dose, and SARS CoV-2 IgG levels were compared between the two groups.
>
> Results: Of 539 pregnant women who were recruited after completion of the 2-dose regimen of the vaccine, 390 returned the digital questionnaire and were included in the study group and compared to 260 age-matched non-pregnant women. The rate of most of the adverse events among pregnant women following vaccination was comparable to non-pregnant women except for myalgia, arthralgia and headache which were significantly less common among pregnant women after each dose and paresthesia, which was more common among the pregnant population after the second dose. There were no significant differences in the rates of side effects when receiving the vaccine at the first, second or third trimester of pregnancy. The rate of obstetrical complications, including uterine contractions (1.3% after the first dose and 6.4% after the second dose), vaginal bleeding (0.2% after the first dose and 1.5% after the second dose), and premature rupture of membranes (0% after the first dose and 0.7% after the second dose) were extremely low following vaccination. All maternal sera samples of both groups were positive for SARS CoV-2 IgG. However, pregnant women had significantly lower serum SARS CoV-2 IgG levels compared to non-pregnant women (27.03 vs 34.5 respectively, $p<0.001$). Among 57 women, who delivered during the study period median gestational age at delivery was 39.5 (IQR 38.7-40.0) weeks with no preterm birth <37 weeks and no cases of fetal or neonatal complications or death.
>
> Conclusions: As shown by the adverse effect profile and short-term obstetric and neonatal outcomes, no safety signals appeared among pregnant women who were vaccinated by BNT162b2vaccine at all stages of pregnancy. The vaccine is effective in generating humoral immune response in pregnant women, although IgG levels were lower than observed in non-pregnant women."

Pediatric Population

Journal Articles

Pediatrics: Six Month Follow-up of Patients With Multisystem Inflammatory Syndrome in Children (28 July 2021)

> "Background and Objectives: Myocardial dysfunction and coronary abnormalities are prominent features of multisystem inflammatory syndrome in children (MIS-C). This study aims to evaluate the early and mid-term outcomes of MIS-C.

> Methods: This is a longitudinal 6-month cohort study of all children admitted and treated for MIS-C from April 17- June 20, 2020. Patients were followed about 2-weeks, 8-weeks and 6-months postadmission, with those with coronary aneurysms evaluated more frequently.
>
> Results: Acutely, 31 (62%) patients required intensive care with vasoactive support, 26 (52%) had left ventricular (LV) systolic dysfunction, 16 (32%) had LV diastolic dysfunction, 8 (16%) had coronary aneurysms (Z-score >/=2.5), and 4 (8%) had coronary dilation (Z-score <2.5). 48 patients (96%) received immunomodulatory treatment. At 2-weeks, there was persistent mild LV systolic dysfunction in one patient, coronary aneurysms in two, and dilated coronary artery in one. By 8-weeks through 6-months, all patients returned to functional baseline with normal LV systolic function and resolution of coronary abnormalities. CMRI performed during recovery in select patients revealed no myocardial edema or fibrosis. Some patients demonstrated persistent diastolic dysfunction at 2-weeks (5, 11%), 8-weeks (4, 9%) and 6-months (1, 4%).
>
> Conclusion: Children with MIS-C treated with immunomodulators have favorable early outcomes with no mortality, normalization of LV systolic function, recovery of coronary abnormalities, and no inflammation or scarring on CMRI. Persistence of diastolic dysfunction is of uncertain significance and indicates need for larger studies to improve understanding of MIS-C. These findings may help guide clinical management, outpatient monitoring, and considerations for sports clearance."

Lancet: Global minimum estimates of children affected by COVID-19-associated orphanhood and deaths of caregivers: a modelling study (20 July 2021)

> "Background: The COVID-19 pandemic priorities have focused on prevention, detection, and response. Beyond morbidity and mortality, pandemics carry secondary impacts, such as children orphaned or bereft of their caregivers. Such children often face adverse consequences, including poverty, abuse, and institutionalisation. We provide estimates for the magnitude of this problem resulting from COVID-19 and describe the need for resource allocation.
>
> Methods: We used mortality and fertility data to model minimum estimates and rates of COVID-19-associated deaths of primary or secondary caregivers for children younger than 18 years in 21 countries. We considered parents and custodial grandparents as primary caregivers, and co-residing grandparents or older kin (aged 60–84 years) as secondary caregivers. To avoid overcounting, we adjusted for possible clustering of deaths using an estimated secondary attack rate and age-specific infection–fatality ratios for SARS-CoV-2. We used these estimates to model global extrapolations for the number of children who have experienced COVID-19-associated deaths of primary and secondary caregivers.
>
> Findings: Globally, from March 1, 2020, to April 30, 2021, we estimate 1 134 000 children (95% credible interval 884 000–1 185 000) experienced the death of primary caregivers,

> including at least one parent or custodial grandparent. 1 562 000 children (1 299 000–1 683 000) experienced the death of at least one primary or secondary caregiver. Countries in our study set with primary caregiver death rates of at least one per 1000 children included Peru (10·2 per 1000 children), South Africa (5·1), Mexico (3·5), Brazil (2·4), Colombia (2·3), Iran (1·7), the USA (1·5), Argentina (1·1), and Russia (1·0). Numbers of children orphaned exceeded numbers of deaths among those aged 15–50 years. Between two and five times more children had deceased fathers than deceased mothers.
>
> Interpretation: Orphanhood and caregiver deaths are a hidden pandemic resulting from COVID-19-associated deaths. Accelerating equitable vaccine delivery is key to prevention. Psychosocial and economic support can help families to nurture children bereft of caregivers and help to ensure that institutionalisation is avoided. These data show the need for an additional pillar of our response: prevent, detect, respond, and care for children."

COVID-19 Vaccines

NEJM: Safety, Immunogenicity, and Efficacy of the BNT162b2 Covid-19 Vaccine in Adolescents (15 July 2021)

> "Background: Until very recently, vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) had not been authorized for emergency use in persons younger than 16 years of age. Safe, effective vaccines are needed to protect this population, facilitate in-person learning and socialization, and contribute to herd immunity.
>
> Methods: In this ongoing multinational, placebo-controlled, observer-blinded trial, we randomly assigned participants in a 1:1 ratio to receive two injections, 21 days apart, of 30 µg of BNT162b2 or placebo. Noninferiority of the immune response to BNT162b2 in 12-to-15-year-old participants as compared with that in 16-to-25-year-old participants was an immunogenicity objective. Safety (reactogenicity and adverse events) and efficacy against confirmed coronavirus disease 2019 (Covid-19; onset, ≥7 days after dose 2) in the 12-to-15-year-old cohort were assessed.
>
> Results: Overall, 2260 adolescents 12 to 15 years of age received injections; 1131 received BNT162b2, and 1129 received placebo. As has been found in other age groups, BNT162b2 had a favorable safety and side-effect profile, with mainly transient mild-to-moderate reactogenicity (predominantly injection-site pain [in 79 to 86% of participants], fatigue [in 60 to 66%], and headache [in 55 to 65%]); there were no vaccine-related serious adverse events and few overall severe adverse events. The geometric mean ratio of SARS-CoV-2 50% neutralizing titers after dose 2 in 12-to-15-year-old participants relative to 16-to-25-year-old participants was 1.76 (95% confidence interval [CI], 1.47 to 2.10), which met the noninferiority criterion of a lower boundary of the two-sided 95% confidence interval

> greater than 0.67 and indicated a greater response in the 12-to-15-year-old cohort. Among participants without evidence of previous SARS-CoV-2 infection, no Covid-19 cases with an onset of 7 or more days after dose 2 were noted among BNT162b2 recipients, and 16 cases occurred among placebo recipients. The observed vaccine efficacy was 100% (95% CI, 75.3 to 100).
>
> Conclusions: The BNT162b2 vaccine in 12-to-15-year-old recipients had a favorable safety profile, produced a greater immune response than in young adults, and was highly effective against Covid-19."

Lancet Infect Dis: Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy children and adolescents: a double-blind, randomised, controlled, phase 1/2 clinical trial (28 June 2021)

> "Background: A vaccine against SARS-CoV-2 for children and adolescents will play an important role in curbing the COVID-19 pandemic. Here we aimed to assess the safety, tolerability, and immunogenicity of a candidate COVID-19 vaccine, CoronaVac, containing inactivated SARS-CoV-2, in children and adolescents aged 3-17 years.
>
> Methods: We did a double-blind, randomised, controlled, phase 1/2 clinical trial of CoronaVac in healthy children and adolescents aged 3-17 years old at Hebei Provincial Center for Disease Control and Prevention in Zanhuang (Hebei, China). Individuals with SARS-CoV-2 exposure or infection history were excluded. Vaccine (in 0·5 mL aluminum hydroxide adjuvant) or aluminum hydroxide only (alum only, control) was given by intramuscular injection in two doses (day 0 and day 28). We did a phase 1 trial in 72 participants with an age de-escalation in three groups and dose-escalation in two blocks (1·5 μg or 3·0 μg per injection). Within each block, participants were randomly assigned (3:1) by means of block randomisation to receive CoronaVac or alum only. In phase 2, participants were randomly assigned (2:2:1) by means of block randomisation to receive either CoronaVac at 1·5 μg or 3·0 μg per dose, or alum only. All participants, investigators, and laboratory staff were masked to group allocation. The primary safety endpoint was adverse reactions within 28 days after each injection in all participants who received at least one dose. The primary immunogenicity endpoint assessed in the per-protocol population was seroconversion rate of neutralising antibody to live SARS-CoV-2 at 28 days after the second injection. This study is ongoing and is registered with ClinicalTrials.gov, NCT04551547.
>
> Findings: Between Oct 31, 2020, and Dec 2, 2020, 72 participants were enrolled in phase 1, and between Dec 12, 2020, and Dec 30, 2020, 480 participants were enrolled in phase 2. 550 participants received at least one dose of vaccine or alum only (n=71 for phase 1 and n=479 for phase 2; safety population). In the combined safety profile of phase 1 and phase 2, any adverse reactions within 28 days after injection occurred in 56 (26%) of 219

> participants in the 1·5 μg group, 63 (29%) of 217 in the 3·0 μg group, and 27 (24%) of 114 in the alum-only group, without significant difference (p=0·55). Most adverse reactions were mild and moderate in severity. Injection site pain was the most frequently reported event (73 [13%] of 550 participants), occurring in 36 (16%) of 219 participants in the 1·5 μg group, 35 (16%) of 217 in the 3·0 μg group, and two (2%) in the alum-only group. As of June 12, 2021, only one serious adverse event of pneumonia has been reported in the alum-only group, which was considered unrelated to vaccination. In phase 1, seroconversion of neutralising antibody after the second dose was observed in 27 of 27 participants (100·0% [95% CI 87·2-100·0]) in the 1·5 μg group and 26 of 26 participants (100·0% [86·8-100·0]) in the 3·0 μg group, with the geometric mean titres of 55·0 (95% CI 38·9-77·9) and 117·4 (87·8-157·0). In phase 2, seroconversion was seen in 180 of 186 participants (96·8% [93·1-98·8]) in the 1·5 μg group and 180 of 180 participants (100·0% [98·0-100·0]) in the 3·0 μg group, with the geometric mean titres of 86·4 (73·9-101·0) and 142·2 (124·7-162·1). There were no detectable antibody responses in the alum-only groups.
>
> Interpretation: CoronaVac was well tolerated and safe and induced humoral responses in children and adolescents aged 3-17 years. Neutralising antibody titres induced by the 3·0 μg dose were higher than those of the 1·5 μg dose. The results support the use of 3·0 μg dose with a two-immunisation schedule for further studies in children and adolescents."

School and Education

J Sch Health: [COVID-19 Transmission during Transportation of 1st to 12th Grade Students: Experience of an Independent School in Virginia]() (20 July 2021)

> Research from EVMS:
>
> "Background: In-school transmission of COVID-19 among K-12 students is low when mitigation layers are used, but the risk of acquiring COVID-19 during school bus transportation is not well defined. Given the operational limitations of many school districts, more data is needed to determine what mitigation is required to keep COVID-19 transmission low during bus transport.
>
> Methods: An independent school in Virginia monitored 1154 students in grades 1 to 12 with asymptomatic PCR testing every 2 weeks from August 24, 2020 to March 19, 2021, during the highest community transmission. Fifteen buses served 462 students while operating at near capacity of 2 students in every seat, using a physical distancing minimum of 2.5 ft, universal masking, and simple ventilation techniques.
>
> Results: A total of 39 individuals were present on buses during their COVID-19 infectious period, which resulted in the quarantine of 52 students. Universal testing and contact tracing revealed no transmission linked to bus transportation.

> Conclusions: This study demonstrates a model for the safe operation of school buses while near capacity. COVID-19 transmission can be low during student transport when employing mitigation including simple ventilation, and universal masking, at minimal physical distances and during the highest community transmission."

Healthcare Workers

News in Brief

"A Medical Resident's COVID-19 Diary — From getting the virus, to giving out the vaccine" (Medpage Today).

Journal Articles

JAMA Netw Open: Effect of Targeted Behavioral Science Messages on COVID-19 Vaccination Registration Among Employees of a Large Health System: A Randomized Trial (28 July 2021)

> "This randomized trial evaluates whether individually addressed emails designed with behaviorally informed features increase COVID-19 vaccination rates….
>
> During the 3-day study period, an individual email nudge caused more than twice as many HCWs to register for a COVID-19 vaccination compared with HCWs in the control condition, with no significant difference between the 2 emails….
>
> Given the large volume of previous COVID-19 vaccine promotion to HCWs, it may seem counterintuitive that a single additional reminder could increase vaccination by late adopters. However, competing demands on attention, behavioral inertia, and unwieldy processes that make it hard to follow through on intentions likely conspire to make a single, timely, targeted reminder helpful. The emails' behavioral features—active choice, appeal to authority, and emphases on scarcity, social norms, and risk recalibration (eAppendix in Supplement 1)—may have contributed to their effect. The 3.17% absolute increase in vaccination appointments we observed is larger than many real-world nudges6 and may be greater among recipients who are less hesitant about receiving the vaccine. "

JAMA Netw Open: Serologic Surveillance and Phylogenetic Analysis of SARS-CoV-2 Infection Among Hospital Health Care Workers (28 July 2021)

> "Question Which hospital health care workers are at increased risk for SARS-CoV-2 infection, and by whom are they infected?

> Findings In this cohort study of 801 hospital health care workers (HCWs), the risk of getting infected with SARS-CoV-2 was nearly 4-fold higher among HCWs on COVID-19 wards compared with HCWs not in patient care. Combined phylogenetic and epidemiological analyses found no patient-to-HCW transmission but several occurrences of HCW-to-HCW transmission.
>
> Meaning These findings suggest that transmission of SARS-CoV-2 between HCWs deserves more consideration in infection prevention practice."

JAMA Netw Open: Individual- and Institutional-level Concerns of Health Care Workers in Canada During the COVID-19 Pandemic: A Qualitative Analysis (27 July 2021)

> "Question What have been the range of concerns and the sources of distress among health care workers in Canada as the COVID-19 pandemic has evolved?
>
> Findings In this qualitative study of a public online COVID-19 forum available for 21 555 employees in a university health network, common concerns relating to the pandemic included risks of contamination, appropriate personal protective equipment, and worker safety. Although these concerns manifested as individual distress, they also intersected with and were reflective of concerns relating to health care institutions' policies, communication practices, and politics.
>
> Meaning The findings suggest that a mismatch between institutional sources of concern and individual-level interventions may affect the uptake of mental health supports even as the level of distress remains high."

Clin Infect Dis: Longitudinal assessment of COVID-19 vaccine acceptance and uptake among frontline medical workers in Los Angeles, California (22 July 2021)

> "Background: Sentiments of vaccine hesitancy and distrust in public health institutions have complicated the government-led COVID-19 vaccine control strategy in the United States. As the first to receive the vaccine, COVID-19 vaccine attitudes among front line workers are consequential for COVID-19 control and public opinion of the vaccine.
>
> Methods: This study employed a repeated cross-sectional survey administered at three time points between September 24 - February 6, 2021 to a cohort of employees of University of California, Los Angeles (UCLA) Health and the Los Angeles County Fire Department (LACoFD). The primary outcome of interest was COVID-19 vaccination intent and vaccine uptake.
>
> Results: Confidence in COVID-19 vaccines and vaccine uptake rose significantly over time. At Survey 1, confidence in vaccine protection was 46.4% among healthcare workers (HCW) and 34.6% among first responders (FR); by Survey 3, this had risen to 90.0% and 75.7%, respectively. At Survey 1, about one-third of participants intended to receive a vaccine as

> soon as possible. By Survey 3, 96.0% of HCW and 87.5% of FR had received a COVID-19 vaccine.
>
> Conclusions: Attitudes towards vaccine uptake increased over the study period, likely a result of increased public confidence in COVID-19 vaccines, targeted communications, a COVID-19 winter surge in LA County, and ease of access from employer-sponsored vaccine distribution."

GME

NEJM: Audio Interview: The Impact of Covid-19 on Trainees and Junior Faculty (22 July 2021)

> "The continuing spread of SARS-CoV-2 remains a Public Health Emergency of International Concern. What physicians need to know about transmission, diagnosis, and treatment of Covid-19 is the subject of ongoing updates from infectious disease experts at the Journal.
>
> In this audio interview conducted on July 20, 2021, the editors are joined by Katrina Armstrong, physician-in-chief at Massachusetts General Hospital, to discuss the effects of the Covid-19 pandemic on residents and junior faculty, both clinicians and researchers."
>
> Downloaded audio file (.mp3) is 43:13 minutes long.

Mental Health, Psychosocial Issues, and Wellness

News in Brief

"PHOTOS: what item is giving you joy in a pandemic? Your beautiful and quirky answers" (NPR).

Journal Articles

JAMA Psychiatry: Association Between Mood Disorders and Risk of COVID-19 Infection, Hospitalization, and Death: A Systematic Review and Meta-analysis (28 July 2021)

> "Question Are preexisting mood disorders associated with higher risk of COVID-19 infection, hospitalization, severe complications, and death?
>
> Findings In this systematic review and meta-analysis of more than 91 million people, individuals with preexisting mood disorders, compared with those without mood disorders, had significantly higher pooled odds ratios for COVID-19 hospitalization and death. There

> were no associations between preexisting mood disorders and risk of COVID-19 infection or severe events.
>
> Meaning These results suggest that individuals with mood disorders should be categorized as an at-risk group for COVID-19 hospitalization and death, providing basis for vaccine prioritization."

JAMA Psychiatry: Association Between Mental Health Disorders and Mortality Among Patients With COVID-19 in 7 Countries: A Systematic Review and Meta-analysis (27 July 2021)

> "Question Is there a significant association between mental health disorders and COVID-19–related mortality?
>
> Findings In this systematic review and meta-analysis of 16 observational studies in 7 countries with 19 086 patients, mental health disorders were associated with increased COVID-19 mortality according to both pooled crude and adjusted odds ratios. Patients with severe mental health disorders had the highest odds ratios.
>
> Meaning These findings suggest that patients with COVID-19 and mental health disorders should be targeted as a high-risk population for severe forms of COVID-19, requiring enhanced preventive and disease management strategies."

Disparities and Health Equity

News in Brief

Long read: "Vaccine inequity: Inside the cutthroat race to secure doses" (AP).

Journal Articles

JAMA Health Forum: US Health Care Relies on Filipinxs While Ignoring Their Health Needs: Disguised Disparities and the COVID-19 Pandemic (23 July 2021)

> "This Viewpoint explains how data aggregation under a single Asian category has hidden the real health and death toll of COVID-19 among Filipinx in the US, especially the large portion of which are frontline health care workers."

Risk, Transmission, and Exposure

News in Brief

"Why some experts recommend upgrading to N95 masks to help fight the delta variant" (WP).

Journal Articles

MMWR: Guidance for Implementing COVID-19 Prevention Strategies in the Context of Varying Community Transmission Levels and Vaccination Coverage (30 July 2021)

> "What is already known about this topic? COVID-19 vaccines authorized in the United States are effective against severe illness and death from SARS-CoV-2 infection; however, current U.S. coverage is uneven. Implementation of layered prevention strategies reduces SARS-CoV-2 transmission.
>
> What is added by this report? Given the spread of the highly transmissible Delta variant, local decision-makers should assess the following factors to inform the need for layered prevention strategies across a range of settings: level of SARS-CoV-2 community transmission, health system capacity, vaccination coverage, capacity for early detection of increases in COVID-19 cases, and populations at risk for severe outcomes from COVID-19.
>
> What are the implications for public health practice? Although increasing COVID-19 vaccination coverage remains the most effective means to achieve control of the pandemic, additional layered prevention strategies will be needed in the short-term to minimize preventable morbidity and mortality."

Communities and organizations should update COVID-19 prevention strategies based on:
Community spread
Health system capacity
Vaccination coverage
Early detection of COVID-19 increases
Populations at risk
High vaccination + Low community spread = Less need for masking and other prevention strategies
CDC.GOV
bit.ly/MMWR72721
MMWR

J Infect Dis: Higher viral load drives infrequent SARS-CoV-2 transmission between asymptomatic residence hall roommates (24 July 2021)

> "Background: The COVID-19 pandemic spread to over 200 countries in less than six months. To understand COVID spread, determining transmission rate and defining factors that increase transmission risk are essential. Most cases are asymptomatic, but they have viral loads indistinguishable from symptomatic people and do transmit SARS-CoV-2 virus. However, they are often undetected.
>
> Methods: Given high residence hall student density, the University of Colorado Boulder established a mandatory weekly screening test program. We analyzed longitudinal data of 6408 students and identified 116 likely transmission events in which a second roommate tested positive within 14 days of the index roommate.
>
> Results: Although the infection rate was lower in single rooms (10%) than in multiple-occupancy rooms (19%), inter-roommate transmission only occurred ~20% of the time. Cases were usually asymptomatic at the time of detection. Notably, individuals who likely transmitted had an average viral load ~6.5-fold higher than individuals who did not (mean Cq 26.2 vs 28.9). Although diagnosed students moved to isolation rooms, there was no difference in time-to-isolation between cases with or without inter-roommate transmission.
>
> Conclusions: This analysis argues that inter-roommate transmission occurs infrequently in residence halls and provides strong correlative evidence that viral load is proportional to transmission probability."

Clin Infect Dis: COVID-19 Outbreak Associated with a Fitness Center — Minnesota, September–November 2020 (23 July 2021)

> "The Minnesota Department of Health investigated a COVID-19 outbreak at a fitness center in Olmsted County, Minnesota. Twenty-three SARS-CoV-2 infections (five employees and 18 members) were identified. An epidemiological investigation supported by whole genome sequencing demonstrated that transmission of SARS-CoV-2 occurred at the fitness center despite following recommended prevention strategies."

JAMA Netw Open: Association Between COVID-19 Exposure and Self-reported Compliance With Public Health Guidelines Among Essential Employees at an Institution of Higher Education in the US (21 July 2021)

> "Question What was the prevalence of SARS-CoV-2 infection and associated protective behaviors among essential employees at an institution of higher education during the first 6 months of the COVID-19 pandemic in the US?
>
> Findings In this cross-sectional study of 508 essential employees, no cases of SARS-CoV-2 infection were verified by quantitative reverse transcriptase–polymerase chain reaction,

> and only 2 participants had measurable seroreactive IgG antibodies. High levels of handwashing and mask wearing were reported at work and outside work, and social distancing was reported significantly less often at work than outside work.
>
> Meaning The findings suggest that compliance with protective behaviors both at work and outside work may be commensurate with the safe operation of complex work environments during a pandemic."

NEJM: Household Transmission of SARS-CoV-2 from Children and Adolescents (21 July 2021)

> Letter to the editor:
>
> "After an outbreak of coronavirus disease 2019 (Covid-19) at an overnight camp, [ed: see Pediatrics article] we conducted a retrospective cohort study involving camp attendees and their household contacts to assess secondary transmission and factors associated with household transmission….
>
> We interviewed 224 index patients who were 7 to 19 years of age and for whom there was evidence of SARS-CoV-2 infection on the basis of molecular or antigen laboratory testing. A total of 198 of these campers (88%) were symptomatic; symptoms developed in 141 of these 198 children or adolescents (71%) after they returned home from camp….
>
> This retrospective study showed that the efficient transmission of SARS-CoV-2 from school-age children and adolescents to household members led to the hospitalization of adults with secondary cases of Covid-19. In households in which transmission occurred, half the household contacts were infected. The secondary attack rates in this study were probably underestimates because test results were reported by the patients themselves and testing was voluntary. In addition, a third of the index patients returned home from camp after the onset of symptoms, when they were presumably not as infectious as they were before and during the onset of symptoms, and two thirds adopted physical distancing because of a known exposure at camp; both of these factors probably reduced the transmission of SARS-CoV-2 in the household. When feasible, children and adolescents with a known exposure to SARS-CoV-2 or a diagnosis of Covid-19 should remain at home and maintain physical distance from household members."

JAMA Netw Open: Association of a High-Efficiency Particulate Air Filter COVID-19 Testing Booth With Testing Capacity, Cost Per Test Acquired, and Use of Personal Protective Equipment (20 July 2021)

> "This quality improvement study compares COVID-19 testing throughput, personal protective equipment use, and cost per test before vs after the introduction of high-efficiency particulate air–filtered, positive-pressure Hexapod personal protection booths at a hospital in Boston, Massachusetts."

Testing and Serosurveillance

Journal Articles

Lancet Digit Health: Anosmia, ageusia, and other COVID-19-like symptoms in association with a positive SARS-CoV-2 test, across six national digital surveillance platforms: an observational study (22 July 2021)

> "Background: Multiple voluntary surveillance platforms were developed across the world in response to the COVID-19 pandemic, providing a real-time understanding of population-based COVID-19 epidemiology. During this time, testing criteria broadened and health-care policies matured. We aimed to test whether there were consistent associations of symptoms with SARS-CoV-2 test status across three surveillance platforms in three countries (two platforms per country), during periods of testing and policy changes.
>
> Methods: For this observational study, we used data of observations from three volunteer COVID-19 digital surveillance platforms (Carnegie Mellon University and University of Maryland Facebook COVID-19 Symptom Survey, ZOE COVID Symptom Study app, and the Corona Israel study) targeting communities in three countries (Israel, the UK, and the USA; two platforms per country). The study population included adult respondents (age 18-100 years at baseline) who were not health-care workers. We did logistic regression of self-reported symptoms on self-reported SARS-CoV-2 test status (positive or negative), adjusted for age and sex, in each of the study cohorts. We compared odds ratios (ORs) across platforms and countries, and we did meta-analyses assuming a random effects model. We also evaluated testing policy changes, COVID-19 incidence, and time scales of duration of symptoms and symptom-to-test time.
>
> Findings: Between April 1 and July 31, 2020, 514 459 tests from over 10 million respondents were recorded in the six surveillance platform datasets. Anosmia-ageusia was the strongest, most consistent symptom associated with a positive COVID-19 test (robust aggregated rank one, meta-analysed random effects OR 16·96, 95% CI 13·13-21·92). Fever (rank two, 6·45, 4·25-9·81), shortness of breath (rank three, 4·69, 3·14-7·01), and cough (rank four, 4·29, 3·13-5·88) were also highly associated with test positivity. The association of symptoms with test status varied by duration of illness, timing of the test, and broader test criteria, as well as over time, by country, and by platform.
>
> Interpretation: The strong association of anosmia-ageusia with self-reported positive SARS-CoV-2 test was consistently observed, supporting its validity as a reliable COVID-19 signal, regardless of the participatory surveillance platform, country, phase of illness, or testing policy. These findings show that associations between COVID-19 symptoms and test positivity ranked similarly in a wide range of scenarios. Anosmia, fever, and respiratory symptoms consistently had the strongest effect estimates and were the most appropriate empirical signals for symptom-based public health surveillance in areas with insufficient

> testing or benchmarking capacity. Collaborative syndromic surveillance could enhance real-time epidemiological investigations and public health utility globally."

Nat Commun: SARS-CoV-2 antibody dynamics and transmission from community-wide serological testing in the Italian municipality of Vo' (19 July 2021)

> "In February and March 2020, two mass swab testing campaigns were conducted in Vo', Italy. In May 2020, we tested 86% of the Vo' population with three immuno-assays detecting antibodies against the spike and nucleocapsid antigens, a neutralisation assay and Polymerase Chain Reaction (PCR). Subjects testing positive to PCR in February/March or a serological assay in May were tested again in November. Here we report on the results of the analysis of the May and November surveys. We estimate a seroprevalence of 3.5% (95% Credible Interval (CrI): 2.8–4.3%) in May. In November, 98.8% (95% Confidence Interval (CI): 93.7–100.0%) of sera which tested positive in May still reacted against at least one antigen; 18.6% (95% CI: 11.0–28.5%) showed an increase of antibody or neutralisation reactivity from May. Analysis of the serostatus of the members of 1,118 households indicates a 26.0% (95% CrI: 17.2–36.9%) Susceptible-Infectious Transmission Probability. Contact tracing had limited impact on epidemic suppression."

Other Infectious Diseases

News in Brief

Careful of that grilled chicken salad… packaged salad greens are linked to a *Salmonella* outbreak (CDC) and fully cooked chicken is linked to a *Listeria* outbreak (CDC).

"How an altered strand of DNA can cause malaria-spreading mosquitoes to self-destruct" (NPR; see also: Nat Commun article).

"U.S. sees first cases of dangerous fungus resistant to all drugs in untreated people" (STAT; see also: MMWR article).

New Approvals

The FDA has approved Vaxneuvance, Merck's pneumococcal 15-valent conjugate vaccine, in adults older that 18 years old for the prevention of invasive pneumococcal disease (Merck).

Another FDA approval: "fexinidazole as first all-oral treatment for both stages of the *Trypanosoma brucei gambiense* form of sleeping sickness (Human African trypanosomiasis) in patients 6 years of age and older and weighing at least 20 kg" (Sanofi).

Monkeypox

"Nigeria reports uptick in confirmed monkeypox cases in 2021" (ONT).

A patient in Texas who traveled from Nigeria has a confirmed case of monkeypox (CDC); contact with that person has resulted in more than 200 people in 27 states being monitored for possible exposure (STAT).

Other Zoonoses

A 10-year old in Colorado has died from complications linked to plague (CDPHE; see also: MMWR article on antimicrobial treatment of plague).

China has identified the first case and death from monkey B virus in a veterinary surgeon (CCDC).

Journal Articles

MMWR: Changes in Influenza and Other Respiratory Virus Activity During the COVID-19 Pandemic — United States, 2020–2021 (23 July 2021)

> "What is already known about this topic? Nonpharmaceutical interventions introduced to mitigate the impact of COVID-19 reduced transmission of common respiratory viruses in the United States.
>
> What is added by this report? Influenza viruses and human metapneumovirus circulated at historic lows through May 2021. In April 2021, respiratory syncytial virus activity increased. Common human coronaviruses, parainfluenza viruses, and respiratory adenoviruses have been increasing since January or February 2021. Rhinoviruses and enteroviruses began to increase in June 2020.
>
> What are the implications for public health practice? Clinicians should be aware of increased circulation, sometimes off season, of some respiratory viruses and consider multipathogen testing. In addition to recommended preventive actions, fall influenza vaccination campaigns are important as schools and workplaces resume in-person activities with relaxed COVID-19 mitigation practices."

MMWR: Sexually Transmitted Infections Treatment Guidelines, 2021 (23 July 2021)

> "These guidelines for the treatment of persons who have or are at risk for sexually transmitted infections (STIs) were updated by CDC after consultation with professionals knowledgeable in the field of STIs who met in Atlanta, Georgia, June 11–14, 2019. The information in this report updates the 2015 guidelines. These guidelines discuss 1) updated recommendations for treatment of Neisseria gonorrhoeae, Chlamydia trachomatis, and

> Trichomonas vaginalis; 2) addition of metronidazole to the recommended treatment regimen for pelvic inflammatory disease; 3) alternative treatment options for bacterial vaginosis; 4) management of Mycoplasma genitalium; 5) human papillomavirus vaccine recommendations and counseling messages; 6) expanded risk factors for syphilis testing among pregnant women; 7) one-time testing for hepatitis C infection; 8) evaluation of men who have sex with men after sexual assault; and 9) two-step testing for serologic diagnosis of genital herpes simplex virus. Physicians and other health care providers can use these guidelines to assist in prevention and treatment of STIs."

Infect Control Hosp Epidemiol: Risk of methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococcus (VRE) acquisition during ambulance transport: A retrospective propensity-score–matched cohort analysis (21 July 2021)

> "Objective: To estimate the relative risk (RR) of developing methicillin-resistant Staphylococcus aureus (MRSA) or vancomycin-resistant Enterococcus (VRE) colonization or infection within 30 days of ambulance transport.
>
> Methods: We performed a retrospective cohort study of patients with a principal diagnosis of chest pain presenting to our emergency department (ED) over a 4-year period. Patients were included if they presented from and were discharged to nonhealthcare locations without being admitted. Encounters were stratified by arrival mechanism: ambulance versus private vehicle. We performed propensity score matching and multivariable logistic regression to estimate the RR for the primary outcome.
>
> Results: In total, 321,229 patients had ED encounters during the study period. After applying inclusion criteria and propensity score matching, there were 11,324 patients: 3,903 in the ambulance group and 7,421 in the unexposed group. Among them, 12 patients (0.11%) had the outcome of interest, including 9 (0.08%) with MRSA and 3 (0.03%) with VRE. The 30-day prevalence of MRSA or VRE was larger in the ambulance group than in the unexposed group: 8 (0.20%) and 4 (0.05%), respectively (P = .02). Patients who presented to the ED via ambulance were almost 4 times more likely to have MRSA or VRE within 30 days of their encounter (RR, 3.72; 95% CI, 1.09-12.71; P = .04).
>
> Conclusions: Our cohort study is the first to demonstrate an association between ambulance exposure and pathogen incidence, representing the first step in evaluating medical-transport-associated infection burden to eventually develop interventions to address it."

MMWR: Antimicrobial Treatment and Prophylaxis of Plague: Recommendations for Naturally Acquired Infections and Bioterrorism Response (16 July 2021)

> "This report provides CDC recommendations to U.S. health care providers regarding treatment, pre-exposure prophylaxis, and postexposure prophylaxis of plague. *Yersinia*

pestis, the bacterium that causes plague, leads to naturally occurring disease in the United States and other regions worldwide and is recognized as a potential bioterrorism weapon. A bioweapon attack with *Y. pestis* could potentially infect thousands, requiring rapid and informed decision making by clinicians and public health agencies. The U.S. government stockpiles a variety of medical countermeasures to mitigate the effects of a bioterrorism attack (e.g., antimicrobials, antitoxins, and vaccines) for which the 21st Century Cures Act mandates the development of evidence-based guidelines on appropriate use. Guidelines for treatment and postexposure prophylaxis of plague were published in 2000 by a nongovernmental work group; since then, new human clinical data, animal study data, and U.S. Food and Drug Administration approvals of additional countermeasures have become available. To develop a comprehensive set of updated guidelines, CDC conducted a series of systematic literature reviews on human treatment of plague and other relevant topics to collect a broad evidence base for the recommendations in this report. Evidence from CDC reviews and additional sources were presented to subject matter experts during a series of forums. CDC considered individual expert input while developing these guidelines, which provide recommended best practices for treatment and prophylaxis of human plague for both naturally occurring disease and following a bioterrorism attack. The guidelines do not include information on diagnostic testing, triage decisions, or logistics involved in dispensing medical countermeasures. Clinicians and public health officials can use these guidelines to prepare their organizations, hospitals, and communities to respond to a plague mass-casualty event and as a guide for treating patients affected by plague."

Statistics

Global 30 JUL 2021:
196,794,025 confirmed cases, 4,202,385 deaths, and 4,034,749,646 vaccine doses administered

United States		top 5 states by cases				
	TOTAL US	CA	TX	FL	NY	IL
Cases	34,756,006	3,944,933	3,120,295	2,523,510	2,144,741	1,417,263
Deaths	612,135	64,386	53,186	38,670	53,625	25,865

JHU CSSE as of 1000 EDT 30 July 2021

Virginia	Total (state)	Chesapeake	Hampton	Newport News	Norfolk	Portsmouth	Suffolk	Virginia Beach
Cases	694,384	21,840	11,005	14,719	18,393	9,399	8,195	37,383
Hospitalizations	31,336	1,064	473	552	1,072	710	491	1,774
Deaths	11,532	311	184	242	274	205	193	421

VA DOH as of 1000 EDT 30 July 2021